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10/677,977	10/02/2003	Jack Nguyen	119357-00007 / 4905	9061

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/677,977	NGUYEN ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11-16,45,48,50-54 and 56-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11-16,45,48,50-54 and 56-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/08, 9/12/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-7, 9, 11-16, 45, 48, 50-54 and 56-66 are pending and under examination in the application.

The typographical error at page 2 (Office action Summery PTO-326 form) wherein claim 2 was indicated to be withdrawn is regretted. As evident from the detailed Office action, pages 3-13, claim 2 was included in all of the rejections.

Withdrawn Rejection

In view of the amendments to the claims and applicants' arguments the 35 USC 112, first and second paragraph and 35 USC 103 rejections in view of Bianchi et al have been withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-7, 9, 11-16, 45-48, 50-54 and 56-66, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over either Harris et al (The Journal of Biological Chemistry)(I) or (Current Opinion in Chemical Biology(II) alone for reasons of record as repeated below.

Harris et al discloses at page 27364, a method of identifying optimal substrate specificity for proteases as granzyme B that allows for the identification of in vivo substrates in the process. The method comprises using the combinatorial methods of synthetic substrate libraries and substrate-phage display for an optimum substrate for granzyme B that spans over six subsites. Granzyme B proteolysis was shown to be highly dependent on the length and sequence of the substrate. Supporting the role of granyzme B preferred substrate sequence matches the activation sites of caspases 3 and 7 that is consistent with the role of granzyme B in the activation of these caspases during apoptosis. Many caspase substrates contain granzyme B cleavage site and are potential granzyme B targets. Harris at page 27364 discloses construction of granzyme B variants of R192A and R192E. Harris (II) throughout the article, at e.g., pages 127-129, basically discloses the same method as Harris (I).

Claims 16, 45-46 and 53 are obvious over the disclosure of Harris of the known iterative process of phage display method.

Response to Arguments

The Examiner did not provide complete citations for the cited references, which Applicant respectfully requests. In the interests of advancing prosecution, however, it is assumed

herein that Harris et al. I is J. Biol. Chem., 273:27364-27373 (1998)), Harris etal. II is Current Opinion in Chemical Biology, 2:127-132 (1998)), and Bianchi et al. is Biopolymers (Peptide Science), 66:101-114 (2002).

In reply, applicants' assumption as to the prior art employed in the rejections, as clearly provided by the cited journal names above and as further evident from the relevant pages cited for each of the above references is correct.

Applicants acknowledge that Harris et al (I) is directed to the screening combinatorial substrate libraries to identify in vivo substrates of rat granzyme B in order elucidate its substrate specificity. Using the combinatorial substrate libraries, Harris et al(I) teaches identification of the optimal P4-P2 substrate specificity profile of granzyme B. Harris et al. I teaches the optimal P4 to P2' granzyme B cleavage site to be (Ile>Val)(Glu>Gln= Met)Xaa-Asp/Xaa-Gly, for example, the substrate sequence IEPD. Harris et al. also teaches identification of in vivo targets of granzyme B based on the elucidation of the substrate specificity of granzyme B. For example, Harris et al. teaches that based on the substrate specificity of granzyme B, certain caspases (caspases 3 and 7), based on their sequences, are more likely substrates then other caspases. Harris et al., also teaches that based on the sequence

specificity of granzyme B, nuclear lamin A and nuclear poly(ADP)ribose polymerase (PARP) are potential in vivo substrates for granzyme B. Harris et al. I also teaches that amino acid position Arginine 192 is a structural determinant of specificity of granzyme B, since granzyme B mutations R192E and R192A exhibit reduced hydrolysis of the optimal tetrapeptide substrate Ac-IEPD-AMC and non-optimal tetrapeptide substrate Ac-IKPD-AMC compared to the wild-type enzyme. But argue that there is no teaching or suggestion in Harris et al. I of a method that includes a step of preparing a library of muteins of a particular protease scaffold, such as granzyme B; then measuring the cleavage activity or substrate specificity of granzyme B muteins in the library for a substrate sequence in a target protein involved in a pathology; and then identifying a library member that has increased cleavage activity and/or substrate specificity for the target compared to the wild-type protease.

In reply, all the elements of the claimed method are discussed by applicants, supra. Attention is drawn to the Harris reference, which discloses, throughout the article, at e.g., page 27365, col. 1, first incomplete paragraph the method of providing mutein library of granzyme B with substrate specificity:

> …Two combinatorial methods to extend the definition of the substrate specificity of granzyme B to six subsites from P4 to P2. Individual amino acids responsible for determining **stringent substrate specificity** of granzyme B were identified through the construction of a three-dimensional model of granzyme B complexed to substrate. **Variant granzyme B with altered P1 and P3 substrate recognition properties were created** (reads on the claimed library) **to define the molecular determinants of specificity** (reads on the claimed altered specificity). The elucidated substrate specificity was shown to be relevant within a macromolecular context by locating cleavage sites in defined molecular targets. (Emphasis added).

Attention is further directed to the Experimental Procedures section commencing at e.g., page 27365, col. 2 which recites the construction of Granzyme B variants (muteins, as claimed), especially the method of creation of P3, P1', P2' his-tagged substrate phage library:

> The vector contains the following amino acid sequence…. residues 198-406 of pIII coat protein of MI3 bacteriophage: AESVQPLGPG.HHHHHHHGHAGIXPDXXAGPGGG….The degenerate oligonucleotides synthesized to create the library consisted of the following sequence (where N indicates equimolar concentrations of G, C, A, and T; S indicates equimolar concentrations of G and C): CAT GGG CAT GCA GGA ATT NNS CCA GAC NNS NNS GCA GGG CCC GGA GGC GGT CCA TTC GTT…. The library of substrate phage has 32,768 possible DNA sequences that translates into 8000 possible protein sequences. Phage particles expressing the engineered pIII-substrate fusion protein were prepared as described previously (26)….Phage particles…. were added to the washed Ni(II) resin and allowed to bind with gentle agitation for 3 h. The Ni(II) resin was then washed…. to remove unbound phage…… the cleaved phage were separated from the resin ….The cleaved phage were amplified….to form recombinant phage which were then usual for the **next round of cleavage selection.** After four rounds of cleavage selection…. Twenty individual colonies were selected and grown…. and plasmld

> DNA was isolated and sequenced in the region of the cleavage site.
> …Rat mast cell protease-2 (RMCP-2) (28) was used as the **framework** (scaffold, as claimed) to model rat granzyme B since they share 49% sequence identity.

The RESULTS section at e.g., pages 27365-27371, including Fig. 1 at page 27366 describes the isolation and purification of granzyme B from the library that has increased cleavage activity and altered substrate specificity e.g., caspase.

Attention is further directed to page 27367:

> A positional scanning combinatorial substrate library (PS-SCL) was used to elucidate the specificity of purified, recombinant, rat granzyme B. This library, of the general structure Ac-Xaap4-Xaam-Xaap2- Asp-AMC, has been previously used to identify the amino acid preferences of the caspases and human granzyme B purified from cultured natural killer leukemia YT cells (27). The PS-SCL is composed of three libraries, each of which consist of 20 sublibraries, for a total of 4000 compounds. In each sublibrary, one position (P4, P3, or P2) contains a defined amino acid and the other two positions contain an equimolar mixture of amino acids (two unnatural amino acids, D-alanine (D-A) and nor leucine (n), are included; eysteine and methionine are excluded). Thus analysis of the three libraries affords a complete understanding of **enzyme preferences for amino acids at P4, P3, and P2.** This approach has been previously validated as providing an accurate measure of protease specificity using caspase-1……The PS-SCL indicates that granzyme B can accept a broad range of amino acids in the P2 position, although proline is the preferred amino acid……..The positional scanning synthetic combinatorial library suggests that granzyme B exhibits unique and extended substrate specificity……(Emphasis added).

See also, Fig. 4, page 27370 as showing the scaffold.

Harris also discloses at e.g., pages 27372 up to and 27373:

> ….{T]here is a functional relationship between the preferential substrate sequence of granzyme B and the activation site of members of the caspases (Fig. 5D). Indeed, studies have shown that granzyme B cleaves and activates several **caspases involved in apoptosis** (reads on target protein involved with a pathology). Our data on the substrate specificity of granzyme B suggest that caspase 3 and caspasc 7 are preferentially activated during apoptosis. Knowledge of the extended substrate specificity of granzyme B allows for the proposal of additional targets of granzyme B during apoptosis. The substrate specificity of caspase 6 matches that of granzyme B (27), suggesting that both enzymes cleave the same substrates. Several proteins known to be cleaved during apoptosis, such as nuclear lamin A….
> The identification of their specificity will further expand our knowledge of the role that granzymes play in **cytotoxic, lymphocyte-mediated cell death.** (Emphasis added).

Accordingly, all the elements of the claimed method are fully described by Harris et al (I).

Applicants argue Harris et al. II does not teach or suggest a method of producing and identifying a protease with increased cleavage activity and/or altered substrate specificity for a target protein involved in a pathology. There is no teaching or suggestion in Harris et al. that a protease having increased cleavage activity and/or substrate specificity for a target protein in a pathology could be used as a treatment. Hence, there is no teaching or suggestion in Harris et al. of modifying a protease to have increased cleavage activity and/or

specificity for a substrate sequence in a target protein involved in pathology nor any methods of doing so.

In response, attention is drawn to Harris et al (II) disclosure throughout the article e.g., at paragraph bridging pages 129 and 130:

> A similar **therapeutic objective** in redesigning pre-existing enzymatic substrate specificity is the creation of 'designer enzymes' to enhance the activity of small molecule drugs... A combination of random mutagenesis, genetic selection and drug-sensitivity screens was used to generate herpes simplex virus type I thymidine kinase (HSV-I TK) variants that demonstrate substrate specificity towards the chain-terminating nucleoside analog pro-drugs ganciclovir and acyclovir. **The preferential phosphorylation of these pro-drugs would increase their chemotherapeutic value in treating particular cancers by enhancing the incorporation of the drug into DNA.** Based on the sequence conservation among the thymidine kinases and previous mutagenesis studies, six amino acids were targeted for saturation mutagenesis. These sites were changed to all other possible amino acids and the resulting **library of randomized HSV-I TKs was sequentially selected for thymidine kinase activity and screened for sensitivity in ganciclovir and acyclovir. A variant with four amino acid substitutions in the kinase active site resulted from the screen that was 43 times more sensitive to ganciclovir and 20 times more sensitive to acyclovir. This approach could provide a potentially useful tool for gene therapy applications.** (Emphasis added).

With respect to the rejection of claims 16, 45-46 and 53 as being obvious over the disclosure of Harris (I or II) applicants assert that neither of these references teaches or suggests an iterative phage display method that displays mutein proteases. Harris et al. I teaches a substrate phage display, but does not

teach or suggest any method for identifying protease muteins, nor any iterative method for identifying protease muteins, in particular protease muteins having an increased cleavage activity and/or altered substrate specificity for a target protein involved in a pathology. Harris et al. II also does not teach or suggest a method of identifying further protease muteins by first identifying those that have increased cleavage activity and/or altered substrate specificity for a substrate sequence in a target protein involved in a pathology, and then either combining the mutations of two of the identified protease(s) to generate a third protease or repeating the method by producing a new library from an identified protease, whereby the further protease muteins have increased cleavage activity and/or altered substrate specificity towards the substrate sequence.

In response, attention is drawn to Harris (1), Experimental Procedures section commencing at e.g., page 27365, col. 2. It describes the well known phage process of iterative selection to obtain e.g., enzymes with increased property e.g., specificity (e.g., the known phage biopanning):

> ….Phage particles…. were added to the washed Ni(II) resin and allowed to bind with gentle agitation for 3 h. The Ni(II) resin was then washed…. to remove unbound phage…… the cleaved phage were separated from the resin ….The cleaved phage were amplified….to form recombinant phage

> which were then use for the **next round of cleavage selection.** After four rounds of cleavage selection….individual colonies were selected and grown…. and plasmld **DNA was isolated and sequenced in the region of the cleavage site.** (Emphasis added).

Claims 1-7, 9, 11-16, 45-48, 50-54 and 56-66, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Koltermann et al (US 2004/0072276) in view of Waugh et al (Nature Structure Biology) for reasons advanced in the last Office action and repeated below.

Koltermann et al discloses throughout the patent at e.g.,:

> [0016] (1) a method for generating sequence-specific proteases with target substrate specificities which comprises the following steps; [0017] (a) providing a population of proteases comprised of variants of one first protease (claim 1)or of variants or chimeras of two or more first proteases,(claim 53) said first proteases having a substrate specificity for a particular amino acid sequence of a first peptide substrate; [0018] (b) contacting said population of proteases with one or more second substrates, comprising at least one specific amino acid sequence resembling the amino acid sequence of the target peptide substrate but being not present within the first peptide substrate; and [0019] (c) selecting one or more protease variants from the population of proteases provided in step (a) having specificity for said specific amino acid sequence of the second substrates provided in step (b) under conditions that allow identification of proteases that recognize and hydrolyze preferably said specific one amino acid sequence within the second substrates; [0024] The identification and selection of proteases that have evolved towards the target specificity is done by screening for catalytic activities on different peptide substrates, either by screening for increased affinity, or by using two substrates in comparison, or by using unspecific peptides as competitors, or by using intermediate peptide substrates..

Koltermann discloses at e.g., paragraph:

> [0059] …any protease can be used as first protease. Preferably, an endoprotease is used as first protease. It is preferred that the protease belongs to the group of proteases consisting of Serine proteases, Cysteine proteases, Aspartic proteases, and Metalloproteases. First proteases are characterized by their ability to recognize and hydrolyze peptide substrates with a certain qualitative and quantitative specificity. First proteases can have specificity in the same range as the specificity of the protease that is to be generated. Examples for proteases with relatively high specificities are TEV protease, HIV-1 protease, BAR1 protease, Factor Xa, Thrombin, tissue-type plasminogen activator, Kex2 protease, TVMV-protease, RSV protease, MuLV protease... Alternatively, the first proteases have a lower specificity than the specificity of the protease that is to be generated. As an extreme example of the latter, proteases with very low sequence specificity are employed, for example proteases such as Papain, Trypsin, Chymotrypsin, Subtilisin, SET (trypsin-like serine protease from Streptomyces erythraeus), Elastase, Cathepsin G or Chymase.

See further the Examples, pages 12-14.

Koltermann does not disclose that the enzyme used in the method is granzyme B, (the elected species). However, Waugh discloses at page 762 that Granzymes are a vial component of the cytotoxic lymphocyte's ability to induce apoptosis, contributing to rapid cell death of a tumor or virally infected target cell by the cleavage of downstream substrates and the activating cleavage of caspases. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use granzyme as the enzyme in the method of

Koltermann as taught by Waugh. One would be motivated to use granzyme for the advantage taught by Waugh above i.e., rapid cell death of a tumor cell.

Response to Arguments

Applicants state that the Examiner did not provide complete citations for the cited reference of Waugh et al, which Applicant respectfully requests. In the interests of advancing prosecution, however, it is assumed herein that the Waugh et al. reference relied upon is Waugh et al., Nature Structure Biology 7:762-765 (2000).

In reply, the above Office action clearly cited the Waugh reference by providing the journal name and relevant sections of the paper's disclosure which applicants have correctly cited.

Applicants recognized that Kolterman et al is directed to a method for generating a sequence-specific protease that recognizes and cleaves a user-definable amino acid sequence with high specificity, such that only cleavage of specific amino acid sequences occurs. The method involves contacting a population of protease variants specific for a first substrate with a second substrate that contains a specific amino acid sequence resembling the target peptide substrate and selecting one or more protease variants that has specificity preferably for the second substrate. Kolterman et al. does not teach or suggest

any specifics of the second substrate, nor of the target peptide substrate, except to provide as a preferred target substrate a substrate of tissue-type plasminogen activator (CPGR/VVGG). In some examples of the method, Kolterman et al. teaches that the substrate has an intermediate sequence compared to the first substrate and the second substrate. In other examples of the method, the second substrate containing the target peptide sequence is incubated with the protease in the presence of an inhibitor. Kolterman et al. teaches that steps of its method can be repeated until one or more protease variants with specificity for the intermediate substrate and/or the target substrate are identified. Kolterman et al. teaches exemplary proteases that can be used in the method, in particular BAR1 protease. But argue that Kolterman et al. does not suggest producing a library of protease muteins of a protease scaffold, where each member of the library has N mutations relative to the wild- type protease scaffold. Nonetheless, applicants recognize that the library of Kolterman et al. contains protease variants specific for a first substrate. But applicants argue that the library used in the method of Kolterman et al. is different from the library used in the instantly claimed methods. Furthermore, the library is contacted with a second substrate that contains a specific amino acid sequence resembling the target peptide substrate or with a

substrate sequence of a target, but in the presence of an inhibitor. In contrast, in the instantly claimed methods, the library is contacted with a target, and the target is one involved in a pathology. The method of Kolterman et al. then includes a step of selecting one or more protease variants that has specificity preferably for the second substrate. In contrast, the instantly claimed methods include a step of identifying at least one mutein protease that has increased cleavage activity and/or altered substrate specificity for cleaving a substrate sequence in the target protein compared to the unmodified protease scaffold. Kolterman et al. does not teach or suggest that the target substrate used in the method is a target substrate involved with a pathology, and particularly a target among the recited targets in independent claim 1, 59, 63 and/or 66. There is no teaching or suggestion of any target substrates used in the method, except a substrate of tissue plasminogen activator. Kolterman et al. does not teach or suggest a method in which the target substrate is a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis, nor any specific proteins recited in independent claims 1, 59 and/or 63.

In reply, applicants' arguments is not commensurate with the elected species of the target protein i.e., caspase.

Kolterman et al. does not teach a method containing a step of identifying protease muteins that have increased cleavage activity and/or altered substrate specificity for the substrate sequence in the target substrate. Kolterman et al. also does not teach a step of the method of combining mutations from identified mutein proteases to generate a third protease, and then measuring the cleavage activity and/or substrate specificity thereof to determine if it is increased or altered compared to the first or second mutein protease. Thus, Kolterman et al. fails to teach or suggest the elements of any and all of the pending claims. Waugh et al. (Nature Structure Biology 7:762-765 (2000) Waugh et al. fails to cure these deficiencies. Applicants acknowledged that Waugh et al. is directed to a description of the structure of granzyme B, and elucidation of the molecular determinants of specificity therefrom. Waugh et al. teaches the residues in granzyme B that play a role in determining substrate specificity as deduced from a three dimensional structure of granzyme B in complex with a macromolecular inhibitor, ecotin. But argue Waugh et al. does not teach or suggest any of the instantly claimed

methods. Waugh et al. fails to teach or suggest a method for producing and identifying a mutein protease that has increased cleavage activity and/or substrate specificity for any target, including any recited in the claims, nor for increasing cleavage activity and/or substrate specificity of granzyme B for any target. Waugh et al. does not teach or suggest any method for modifying granzyme B so that has increased cleavage activity and/or substrate specificity for any target compared to unmodified granzyme B. Hence, there is no teaching or suggestion of a method for identifying mutant proteases that have increased cleavage activity and/or altered substrate specificity for a target substrate involved in a pathology, which protease could be used to treat the pathology. There is no teaching or suggestion in Waugh et al. that modified granzyme B would exhibit altered substrate specificity or increased cleavage activity, nor any teaching or suggestion of methods of modifying granzyme B to do so, nor any modified granzyme B polypeptides.

In reply, applicants cannot attack the references individually when the rejection is based on the combination of references. Waugh is not employed for the purpose as argued. Rather Waugh is employed for its teaching of granzyme B and the

reason one having ordinary skill in the art would have been motivated to use the enzyme used by Kolterman and replace it with granzyme B as taught by Waugh. The test for combining references is not what the individual references themselves suggest but rather what the combination of the disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 CCPA 1971. The court must approach the issue of patentability in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all the relevant teachings in the art, not in view of the first one and then another of the isolated teachings in the art. In re Kuderna, 165 USPQ 575 CCPA 1970.

Thus, the combined teachings of Kolterman and Waugh will lead one having ordinary skill in the art to the claimed method.

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007).

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0751. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/677,977	NGUYEN ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	